In This Issue

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A brief summary of the articles appearing in this issue of *Biological Psychiatry*.

Adulthood Effects of Adolescent Substance Use

Evidence indicates that some, but not all, adolescents who use cannabis will develop impaired attention and memory in adulthood, which suggests an individual-level vulnerability to the adverse effects of cannabis. Using a rodent model to investigate the underlying molecular mechanisms, **Jouroukhin *et al.*** (pages 891–903) report that a rare *Disc1* mutation in astrocytes but not neurons exacerbates a cannabis-activated inflammatory response, leading to elevated secretion of glutamate by astrocytes, abnormalities in gamma-aminobutyric acid neurons, and long-lasting cognitive deficits, which were prevented with an anti-inflammatory treatment. These data suggest that astrocyte genetic risk factors may interact with adolescent cannabis use to produce cognitive impairment and may thus represent a target for treatment.

Evidence suggests that exposure to alcohol during adolescence may contribute to risk for anxiety disorders in adulthood. Enhancer RNAs (eRNAs) are noncoding RNAs that play a role in the regulation of synaptic plasticity–associated gene expression, including *Arc*. **Kyzar *et al.*** (pages 904–914) report that adult rats with adolescent intermittent ethanol (AIE) exposure show decreased synapse number and expression of *Arc* eRNA in the amygdala and increased anxiety-like behavior. Acute alcohol exposure reversed these changes. Further, knockdown of *Kdm6b* or *Arc* eRNA in the amygdala of alcohol-naïve rats led to the same molecular and epigenetic changes observed in AIE rats. Taken together, these results indicate that epigenetic alterations resulting in decreased *Arc* eRNA may be critical for the increased risk of anxiety in adulthood after AIE exposure.

Intermittent-Access Model of Cocaine Addiction

Cocaine seeking increases in a time-dependent manner after withdrawal, a phenomenon termed incubation of cocaine craving. Using male and female rats, **Nicolas *et al.*** (pages 915–924) examined the effect of intermittent-access cocaine self-administration, a model that more closely mimics the pattern of human cocaine intake, on incubation of cocaine craving. Compared with the standard continuous-access cocaine self-administration procedure, the authors found that the intermittent-access procedure potentiated incubation of cocaine craving, and this effect was greater in female rats. Increased craving in female rats was dependent on the estrous cycle phase, demonstrating a novel role of ovarian hormones in the incubation of cocaine craving.

The orexin system plays a role in reward-driven motivation and has been implicated in addiction-related behavior. Using differential cocaine access conditions in rats, **James *et al.*** (pages 925–935) assessed orexin system function. The authors report that the intermittent-access model produced a multifaceted set of addiction-like behaviors that reflect key diagnostic criteria for addiction in humans and was associated with long-term changes in the number and activity of orexin/hypocretin cells in the lateral hypothalamic subregion. Reducing the signaling of these cells reversed the expression of addiction-related behaviors.

Model-Free and Model-Based Learning in Addiction

Substance-dependent individuals show disrupted decision-making processes. Here, **Groman *et al.*** (pages 936–945) used a translationally inspired variant of a multistage decision-making task in rats before and after methamphetamine self-administration to determine the role of distinct reinforcement learning processes known to guide decision making in addiction-related pathology. They found that preexisting differences in reward-driven, model-free behavior predicted drug self-administration and that both model-free and model-based learning were independently reduced following methamphetamine self-administration. These data demonstrate that distinct reinforcement learning systems are involved in diverse aspects of addiction vulnerability and pathology.

Exome-wide Meta-analysis of Nicotine and Alcohol

Common genetic variants in multiple loci have been associated with smoking and alcohol use. Advances now permit the efficient investigation of rare and low frequency variants. **Brazel *et al.*** (pages 946–955) conducted an exome-wide meta-analysis and identified 171 genomic loci associated with nicotine and alcohol use phenotypes. Analyses attributed 11% to 18% of the total single nucleotide polymorphism heritability of these substance use phenotypes to rare coding variants. Additionally, fine-mapping analysis identified specific variants within these loci that contribute to substance use behavior.

Inhibitory Control: A Biomarker of Disordered Eating

Eating disorders typically develop during adolescence and are associated with poor inhibitory control, but the underlying neural correlates remain unclear. Using prospective longitudinal data from an adolescent cohort, **Bartholdy *et al.*** (pages 956–965) report that adolescents who developed disordered eating behaviors at follow-up showed increased medial prefrontal cortex and anterior cingulate cortex activity during failed inhibitory control at baseline, compared with both healthy control subjects and recovered participants who had reported disordered eating behaviors at baseline only. These data suggest that neural markers of failed inhibition precede symptom development and thus may serve as a useful risk biomarker.

Striatal Connectivity and Clinical Symptom Domains

Neurodevelopment of corticostriatal circuits is critical for establishing diverse cognitive functions. Despite this, striatal development and its role in the etiopathogenesis of psychopathology remain poorly understood. Here, **Barber *et al.*** (pages 966–976) characterized maturation of striatal functional subdivisions in a general-population developmental cohort. The authors identified associations with unique and overlapping striatal connections for attention-deficit/hyperactivity disorder, psychosis, depression, and general psychopathology clinical symptom domains. These data provide insight into the aberrant neurodevelopmental processes that may contribute to clinical risk.

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